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Central Nervous System Tuberculosis: Pathogenesis and Clinical Aspects

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INTRODUCTION

Central nervous system (CNS) disease caused by *Mycobacterium tuberculosis* is an uncommon yet highly devastating manifestation of tuberculosis, which was universally fatal in the era before antituberculosis therapy. CNS tuberculosis accounts for approximately 1% of all cases of tuberculosis, carries a high mortality and a distressing level of neurological morbidity, and disproportionately afflicts children and human immunodeficiency virus (HIV)-infected individuals. Due to its relative rarity and the protean nature of the symptoms, tuberculosis of the CNS remains a formidable diagnostic challenge. Because the burden of CNS tuberculosis lies largely in resource-starved regions of the world, additional challenges in implementing practical and usable methods to diagnose and treat this disease remain largely unmet.

While other clinical manifestations of tuberculosis have received considerable research attention, fundamental questions regarding the pathogenesis, diagnosis, treatment, and management of CNS tuberculosis remain unanswered. What is the best way to diagnose CNS tuberculosis? What is the optimal treatment for this disease? How can we mitigate the significant neurological morbidity among survivors? How can we more rapidly diagnose CNS tuberculosis? These questions remain open. Because infection with *M. tuberculosis* afflicts primarily humans, in order to advance our understanding of the neuropathogenesis of *M. tuberculosis*, the need for an appropriate animal model is paramount. Although several animal models have been described, none truly mimics human infection.

The purpose of this review is to highlight the current understanding of the neuropathogenesis of *M. tuberculosis* and to discuss certain epidemiological, clinical, diagnostic, and therapeutic aspects of CNS tuberculosis.

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EPIDEMIOLOGY

In 2005, there were an estimated 8.8 million new cases of active tuberculosis reported annually, resulting in an estimated

1.6 million deaths per year (242). Tuberculosis remains a worldwide burden, with a large majority of new active tuberculosis cases occurring in underdeveloped and developing countries (242). In 80% of new tuberculosis cases, demographic factors such as poverty, crowding, malnutrition, and a compromised immune system play a major role in the worldwide epidemic, while the remaining 20% of tuberculosis cases are associated with HIV in sub-Saharan Africa (235, 242).

Infection of the CNS is one of the most devastating clinical manifestations of tuberculosis. In a large-scale epidemiological study of extrapulmonary tuberculosis in the United States, CNS involvement was noted in 5 to 10% of extrapulmonary tuberculosis cases (172), with more recent CDC data in 2005 indicating that 6.3% of extrapulmonary cases (1.3% of total tuberculosis cases) involve the CNS (31). In the largest prospective epidemiological study on CNS tuberculosis, the chance of developing CNS tuberculosis was 1.0% among 82,764 tuberculosis cases from 1970 to 2001 in a Canadian cohort (157).

Several risk factors for CNS tuberculosis have been identified. Both children (56) and HIV-coinfected patients (14, 52, 169) are at high risk for developing CNS tuberculosis. Other risk factors include malnutrition and recent measles in children (246) and alcoholism, malignancies, and the use of immunosuppressive agents in adults (101, 143, 233). Studies conducted in developed countries have also identified that foreign-born individuals (individuals born outside of developed countries) are overrepresented among CNS tuberculosis cases (19, 157).

Looking at the impact of CNS tuberculosis, a study in Spain documented that CNS tuberculosis accounted for 3.2% of tuberculosis deaths in 1993 (the rate was 0.06), a rate that had steadily declined over the previous 20 years (60). In a large study in Taiwan, Lu et al. reported that 1.5% of tuberculosis deaths between 1997 and 2001 were attributable to CNS disease, a percentage that had increased from previous years (118).

PATHOGENESIS OF TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM

Overview of Pathogenesis

M. tuberculosis is an aerobic, nonmotile, non-spore-forming, acid-fast bacillus (AFB) that infects primarily humans. Its doubling time is quite slow (15 to 20 h) and requires several weeks to grow on conventional Löwenstein-Jensen medium, where it tends to grow in parallel groups, producing the colonial characteristic of serpentine cording. Biochemical as well as RNA/DNA-based methods can identify *M. tuberculosis* from other AFB.

The acquisition of *M. tuberculosis* infection occurs through the inhalation of droplet nuclei containing the bacilli, eventually leading to deposition in the lung alveoli. Once in the alveoli, the bacilli interact with alveolar macrophages through a multitude of different receptors (15, 53, 113, 158, 232). Once these innate immune cells are triggered, numerous cytokines and chemokines are released, the activation of a type 1 T-helper cell-mediated immune response occurs, and, ultimately, a granuloma is formed. Early in this process, prior to the actual containment of the infection, bacilli are filtered into draining lymph nodes, and there exists a low-level bacteremia in which *M. tuberculosis* disseminates to distant sites in the body (177). This hematogenous seeding occurs most frequently in regions of the body that are highly oxygenated, including the brain. A complex interplay of host immune factors and *M. tuberculosis* virulence factors in the end determines whether or not the infection is contained and whether, or to what extent, the dissemination of the bacilli leads to clinical disease (177).

For CNS tuberculosis, the disease begins with the development of small tuberculous foci (Rich foci) in the brain, spinal cord, or meninges. The location of these foci and the capacity to control them ultimately determine which form of CNS tuberculosis occurs. CNS tuberculosis manifests itself primarily as tuberculous meningitis (TBM) and less commonly as tubercular encephalitis, intracranial tuberculoma, or a tuberculous brain abscess (177).

Our understanding of the pathogenesis of TBM comes mainly from the meticulous studies that Rich and McCordock conducted at the Johns Hopkins Hospital and reported in 1933 (171). Using guinea pigs and rabbits, Rich and McCordock showed that the meninges could not be directly infected by the hematogenous spread of the bacilli but rather required the direct inoculation of bacilli into the CNS in order to produce TBM in these animals. By performing a series of postmortem examinations, Rich and McCordock went on to report that in nearly every case, there was a meningeal focus where bacilli gained access to the subarachnoid space and induced meningitis. Based largely on these seminal observations and additional corroborating studies (20, 49, 119), it is generally accepted that a caseating vascular focus, the "Rich focus," in the brain cortex or the meninges is the key pathway for the tubercle bacilli to enter the subarachnoid space (70). This method of entry is in contrast to the direct hematogenous spread typically observed in acute bacterial meningitis.

Soon after Rich and McCordock reported their conclusions, a concern was raised that this mode of entry does not explain the frequent association of miliary tuberculosis and TBM (70, 119). Donald et al. (49) reexamined the original publications and subsequent publications on this matter and concluded that disseminated tuberculosis plays an important role in the development of TBM in children, inasmuch as disseminated tuberculosis increases the probability that a Rich focus will develop, thus enhancing the chances of a fortuitous rupture of the lesion, leading to clinical TBM (70).

The cytokine tumor necrosis factor alpha (TNF-α) is critical in the neuropathogenesis of *M. tuberculosis* (42, 124, 221, 224). Although TNF-α plays a definitive role in granuloma formation and containment of mycobacterial infections (58, 99), local CNS production of TNF-α in experimental bacterial meningitis leads to altered blood-brain barrier (BBB) permeability and cerebrospinal fluid (CSF) leukocytosis (168, 178, 179) and has been implicated in fostering the progression of TBM in a murine model (224).

A distinctive characteristic of *M. tuberculosis* is its capacity to enter and replicate within macrophages. Within the CNS, microglial cells are the resident macrophages, and as such, human microglial cells are productively infected with *M. tuberculosis* and are the principal target in the CNS (42, 173). In our laboratory, we have found that the exposure of purified human microglia and astrocytes to *M. tuberculosis* is associated with a

selective infection of microglia (174) and that the ingestion of nonopsonized *M. tuberculosis* by human microglia is facilitated by the CD14 receptor (153), although this appears not to be the case with human monocyte-derived macrophages (191). This receptor, along with the β_2-integrin CD-18 and TNF-α, is also involved in the formation of histologically characteristic multinucleated giant cells seen at autopsy and experimentally identified in porcine microglia infected with *Mycobacterium bovis* (152). *M. tuberculosis*-infected microglia also produce robust amounts of several cytokines and chemokines in vitro, including TNF-α, interleukin-6 (IL-6), IL-1β, CCL2, CCL5, and CXCL10 (174). One study demonstrated that human microglia are more efficient at ingesting *M. tuberculosis* than virulent and avirulent strains of *M. avium* and that following infection, there is a lasting inhibition of both IL-1 and IL-10 production (42). The authors of that study suggested that mycobacterial infection induces immunosuppressive effects on microglial cells, which is more evident with more virulent strains. From these observations, microglia have emerged as being key cells for understanding the neuropathogenesis of tuberculosis.

In Vitro Models of CNS Tuberculosis

The mechanism by which *M. tuberculosis* crosses the BBB into the CNS is not well characterized. Some have postulated that free bacilli traverse across the endothelial barrier, while others suggested that bacilli enter via the passage of infected macrophages. One method of examining this question is to develop an in vitro model of the BBB and evaluate how *M. tuberculosis* interacts with this barrier. Adapting an in vitro model used for examining other bacteria that cause meningitis (98), Jain et al. used an in vitro monolayer of human brain microvascular endothelial cells and infected them with several strains of mycobacteria (75). They reported that *M. tuberculosis* H37Rv and CDC1551 were able to invade and traverse the endothelial monolayer, thus supporting the notion that extracellular mycobacteria are capable of traversing these highly specialized endothelial cells. However, while their in vitro model utilized brain microvascular endothelial cells, cells that form the brain side of the BBB (mainly astrocytes) were not included in the model, and thus, it is unclear what role these cells play in defense against entry into the brain parenchyma. Despite this, the model proposed by Jain et al. will go a long way toward understanding the important interaction of mycobacteria and endothelial cells.

Animal Models of CNS Tuberculosis

Originating with Rich and McCordock's experimentation with guinea pigs and rabbits (171), over the years, there have been numerous attempts to create an animal model for TBM in an effort to provide a platform for researchers to investigate the neuropathogenesis of *M. tuberculosis*. In 1998, Tsenova et al. described a rabbit model of acute mycobacterial meningitis by introducing *M. bovis* Ravenal (which is virulent in rabbits) by intracranial injection. In their rabbit model, they were able to produce an acute inflammatory response in the CSF, culture viable mycobacteria from the CSF, demonstrate clinical signs of meningitis in the rabbits, identify granulomatous meningitis by histopathological examination, identify viable mycobacteria in other organs, and demonstrate mortality within the 8 days of follow-up (227). Subsequently, other mycobacterial species were studied in this model as well (224). While this model mimics many of the clinical and pathological features of TBM in humans, it also produced acute meningitis, and the course of disease was much more rapid than that of human TBM.

To address the issue of rapid progression in their rabbit model, that same group later reduced the concentration of *M. bovis* Ravenal injected intracranially and produced a subacute model of TBM (226). In this modified model, clinical signs developed in the third week postinoculation, and by 28 days, nearly all of the rabbits were dead or neurologically impaired. Those authors were also able to demonstrate survival among infected rabbits with treatment. In terms of inducing an inflammatory response and recovering viable bacilli in the CSF and elsewhere, the subacute model mirrored the acute model.

That group went on to use this model to evaluate the efficacy of a recombinant polypeptide vaccine (225), demonstrate the importance of TNF-α for the progression of TBM (224), and evaluate the potential role of thalidomide and its analogues in the course of TBM (226, 227).

In 2002, Mazzolla et al. reported that by inoculating BALB/c and DBA/2 mice with *M. bovis* BCG Montreal by intracranial injection, they were able to detect mononuclear infiltration, microglial activation, and mycobacterial growth in the CSF (127). However, discussion of neurological signs or mortality was absent from this report. Although those authors were not reporting the development of a true meningitis model, they did demonstrate a clear difference in the responses of the two different mouse strains.

More recently, van Well et al. described the development of a murine model for the study of TBM (231). They reported that the intracranial inoculation of the virulent *M. tuberculosis* laboratory strain H37Rv into C57BL/6 mice induced a neuroinflammatory response leading to lymphocytic infiltration around the meninges and the perivascular area. In addition, they were able to recover bacilli from murine brain homogenates, although not from the CSF itself, and also detect elevated chemokine levels in the CSF. However, they did not observe any neurological signs of meningitis, did not see any alterations in CSF cytokine production, did not identify granuloma formation on histology, and did not observe any mortality over the 24 weeks of the study. As TBM is almost always fatal, the relevance of this model to CNS tuberculosis in humans is questionable.

Having developed a swine model of human tuberculosis and observing the development of TBM in some animals (22), we have been interested in extending our in vitro work to this swine model, as the immune system of swine is similar to that of humans. However, practical issues imposed by working with infected pigs have led our laboratory to consider developing a murine model to study the pathogenesis of TBM. Following intracranial inoculation of *M. tuberculosis* H37Rv into FVBN mice, we were able to demonstrate robust lymphocytic infiltration around the meninges (Fig. 1) as well as perivascular infiltration within the parenchyma. In addition, we were able to identify granuloma formation within the parenchyma and detect bacilli within the granuloma. However, like van Well et al., we did not observe any mortality within the 3 months of study,

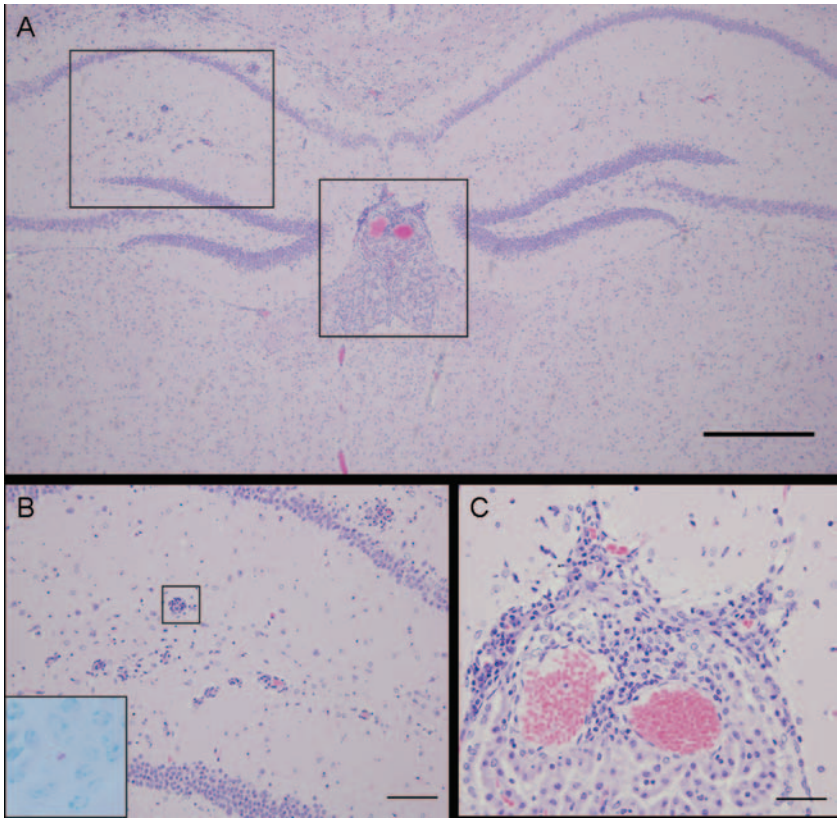

FIG. 1. Murine model of CNS tuberculosis. (A) Coronary section at the level of the caudal diencephalon, with multifocal nonsuppurative encephalitis. Hematoxylin and eosin (HE) staining was used. Bar, 500 μm. (B) Cornu ammonis showing mild perivascular lymphocytic and histiocytic infiltration, with microgliosis and reactive astroglia. HE staining was used. Bar, 100 μm. The inset shows *M. tuberculosis* bacillus in a perivascular macrophage. Acid-fast staining was used. Magnification, ×600. (C) Dorsal third ventricle, choroid plexus, and subependymal areas expanded by lymphocytic, plasmacytic, and histiocytic infiltration, with subependymal microgliosis and reactive astroglia. HE stain. Bar, 50 μm. (Courtesy of Anibal Armien.)

raising the issue of a species tropism barrier to the development of CNS tuberculosis in mice.

To date, looking at the available animal models for TBM, the rabbit model has proven to most closely mimic human disease and therefore, arguably, is the most relevant model. While this model shows clear clinical and histological evidence of disease, unfortunately, a number of immunological tools are unavailable for studies of rabbits, suggesting that continued work on developing a murine model of CNS tuberculosis is worthwhile.

PATHOLOGY

TBM

After the release of tubercle bacilli from granulomatous lesions into the subarachnoid space, a dense gelatinous exudate forms; it is most florid in the interpeduncular fossa and suprasellar region anteriorly, and it may extend throughout the prepontine cistern and surround the spinal cord. This exudate envelops arteries and cranial nerves, creating a bottleneck in the flow of cerebrospinal fluid at the level of the tentorial opening, which leads to hydrocephalus. The exudate contains erythrocytes, neutrophils, and macrophages, followed by lymphocytes in more mature exudates. The Rich foci typically follow the vascular pattern and are located both in the meninges and in the brain parenchyma. Of note, Rich foci are not preferentially distributed to the basilar areas of the brain where the exudate is typically located. The localization of the tuberculous exudate to the basilar area is hypothesized to be simply a result of the normal flow pattern of CSF (171).

The most serious consequence of TBM, however, is the development of vasculitis in the vessels of the circle of Willis, the vertebrobasilar system, and the perforating branches of the middle cerebral artery, resulting in infarctions in the distribution of these vessels. Direct contact of the exudate with the brain surface causes a border zone reaction that damages the underlying brain tissue. Rich and McCordock ascribed most of these changes to a hypersensitivity response (49, 171).

Tuberculoma

Tuberculomas are thought to arise when tubercles in the brain parenchyma enlarge without rupturing into the subarachnoid space. As such, they often occur in the absence of TBM but certainly may occur along with TBM. They more commonly arise as solitary lesions, but multiple tuberculomas are seen. Tuberculomas of the brain show a typical granulomatous reaction consisting of epithelioid cells and giant cells mixed with

TABLE 1. British Medical Research Council clinical criteria for the severity of TBM[a]

Stage/grade	Classic criterion[b]	Contemporary criterion[c]
I	Fully conscious and no focal deficits	Alert and oriented without focal neurological deficits
II	Conscious but with inattention, confusion, lethargy, and focal neurological signs	Glasgow coma score of 14-11 or 15 with focal neurological deficits
III	Stuporous or comatose, multiple cranial nerve palsies, or complete hemiparesis or paralysis	Glasgow coma score of 10 or less, with or without focal neurological deficits

[a] See reference 128.
[b] Data adapted from references 64 and 93.
[c] Data adapted from references 220 and 222.

predominantly lymphocytes around a central area of caseating necrosis. Any liquefaction of the central area of necrosis contains clear or straw-colored fluid, as opposed to pus (108).

Tuberculous Brain Abscess

Brain abscess formation is a rare manifestation of CNS tuberculosis. Tuberculous brain abscess develops either from parenchymal tubercular granulomas or via the spread of tuberculous foci from the meninges and is characterized by an encapsulated collection of pus containing viable bacilli without evidence of the classic tubercular granuloma and must be distinguished from granuloma with central caseation and liquefaction mimicking pus (108). Brain abscesses can arise as solitary or multiple lesions (241). Grossly and radiographically, a tuberculous brain abscess has a much thicker abscess wall than a pyogenic brain abscess (108). Histopathological findings suggest that the inflammatory reaction in the abscess wall is predominantly vascular granulation tissue containing acute and chronic inflammatory cells and bacilli in the pus or abscess wall (241).

CLINICAL FEATURES

Adults with TBM often present with the classic meningitis symptoms of fever, headache and meningismus (stiff neck) along with focal neurological deficits, behavioral changes, and alterations in consciousness (207). Often, a history of or current positive tuberculin skin test, history of exposure to tuberculosis, or the identification of particular risk factors for tuberculosis raises the concern of TBM, although a history of tuberculosis is elicited in only approximately 10% of patients (207). The presence of active pulmonary tuberculosis on chest X ray ranges from 30 to 50% in recent series (207, 217). Patients coinfected with HIV do not appear to have an altered presentation of TBM (14, 52, 217).

Children with TBM often present with fever, stiff neck, seizures, and abdominal symptoms such as nausea and vomiting (57, 246). Headache occurs less often than in adults. Depending on the stage of presentation, neurological symptoms range from lethargy and agitation to coma. Wallgren et al. determined that TBM in children develops most often within 3 months of primary tuberculosis infection (as cited in reference 49). A family history of tuberculosis can be identified in approximately 50 to 60% of children, and a positive tuberculin skin test is found in approximately 30 to 50% (57, 246). In children particularly, there appears to be a close association with disseminated (miliary) tuberculosis, which some have postulated is due to the fact that the robust hematogenous dissemination increases the likelihood that a Rich focus will develop and ultimately rupture (49). In children, the symptoms of TBM often have a quicker pace, and they often seek medical attention within hours to weeks of the onset of symptoms. Some pediatric experts recommend that all children under 12 months of age should have a lumbar puncture due to the susceptibility of this population to disseminated tuberculosis and TBM as well as the difficulty in clinically evaluating infants for TBM. Although it could also be argued that other high-risk, difficult-to-evaluate patients, such as patients with advanced HIV coinfection, also undergo lumbar puncture when diagnosed with tuberculosis, generally, CNS symptoms will guide the clinician to include a lumbar puncture as part of the workup.

Clinical signs of patients presenting with TBM can be easily assessed for severity based on modifications of the Medical Research Council staging system (128) (Table 1), which has been shown in numerous series to have considerable prognostic value (64, 74, 97, 220). The classical staging system is as follows: stage I is fully conscious and no focal deficits; stage II is conscious but with inattention, confusion, lethargy, and focal neurological signs such as cranial nerve palsies; and stage III is stuporous or comatose, multiple cranial nerve palsies, or complete hemiparesis or paralysis (64, 93). A more contemporary modification of the staging system defines grade I as alert and oriented without focal neurological deficits, grade II as a Glasgow coma score of 11 to 14 or 15 with focal neurological deficits, and grade III as a Glasgow coma score of 10 or less with or without focal neurological deficits (220, 222).

Clinical manifestations of tuberculoma or tuberculous brain abscess depend largely on their location, and patients often present with headache, seizures, papilledema, or other signs of increased intracranial pressure. The pace of symptom development usually is measured in weeks to months with tuberculomas. The presentation of brain abscess is more acute (1 week to 3 months) than tuberculoma but slower in onset than pyogenic brain abscesses and is associated with fever, headaches, and focal neurological deficits (108).

DIAGNOSIS

Traditional CSF Analysis

Cytology. The typical analysis of CSF from patients with CNS tuberculosis demonstrates a moderate lymphocytic pleocytosis, moderately elevated protein levels, and hypoglycorrachia (low glucose) (79, 207, 233). As such, the CSF profile of CNS tuberculosis mimics the profiles of a large list of both

TABLE 2. Performance of staining and culture techniques for AFB

Technique[a]	Population	% Sensitivity	Reference
AFB staining			
Ziehl-Neelson with large vol (10–20 ml) and centrifugation (30 min)	100 English pediatric TBM cases	91	201
Ziehl-Neelson with multiple samples	52 American TBM cases	87	96
Not indicated	45 American TBM cases	10	143
Cisternal/ventricular CSF	12 French adult TBM cases	42	233
Ziehl-Neelson	61 Turkish adult TBM cases	19.6	207
Ziehl-Neelson with large vol (6 ml) and 30 min examination	132 Vietnamese adult TBM cases	58	215
AFB culture			
Ziehl-Neelson with multiple samples	52 American adult and pediatric TBM cases	83	96
Not indicated	45 American TBM cases	40	143
Cisternal/ventricular CSF	12 French adult TBM cases	50	233
Löwenstein-Jensen medium	61 Turkish adult TBM cases	11	207
Large vol (6 ml) and 30 min examination	132 Vietnamese adult TBM cases	71	215

[a] Listed from oldest to newest.

infectious and noninfectious processes that affect the CNS. One series of non-HIV-infected adult cases of CNS tuberculosis in Turkey found a CSF lymphocyte predominance in 85%, neutrophil predominance in 15%, high protein levels in 77%, hypoglycorrachia in 67.2%, and elevated opening pressure in 54% of patients (207). Similar results among a series of pediatric cases were also noted (246), and coinfection with HIV does not appear to alter the CSF profile (217). Although hypoglycorrachia is common in both bacterial meningitis and TBM, its presence may provide a convenient discriminating feature that distinguishes these etiologies from most other causes of meningoencephalitis, especially when considering the initiation of empirical antibiotics (216). The predominance of neutrophils in some cases likely represents an earlier stage of infection, which, over the course of days to weeks, will convert to a predominantly lymphocytic profile (79). Rarely, normal CSF findings have been identified in patients ultimately diagnosed with TBM (43). It has been observed that the CSF can later briefly switch to neutrophil predominance with antituberculosis therapy (207). It has been postulated that this "paradoxical response" is due to a hypersensitivity reaction related to the release of tubercular proteins during antituberculosis therapy and, in at least one retrospective series, was related to the development of tuberculomas on therapy (207).

Microbiology. Identification of AFB in the CSF through both smear and culture methods remains the most important and most widely available means to diagnose CNS tuberculosis. Beyond the diagnostic value of these methods, the importance of obtaining a culture is that growth of *M. tuberculosis* in culture allows drug sensitivity testing, which can have a large impact on appropriate drug selection and prognosis. Despite its importance among the diagnostic methods used for CNS tuberculosis, traditional staining and culture remain relatively insensitive, most likely due to the typical paucity of AFB in a clinical case of CNS tuberculosis (Table 2). Standard staining techniques using such stains as Ziehl-Neelsen, Kinyoun, or auramine-rhodamine applied to CSF samples have been estimated to detect approximately 100 AFB/ml of CSF (233). Several case series have established CSF staining sensitivities of <20% (37, 144, 207). As one could anticipate, the actual sensitivity of AFB staining of the CSF at any given laboratory is highly variable, and the inability of more recent series to reflect the yield that older series were able to achieve may reflect the loss of the art of AFB staining. Techniques to improve the sensitivity of AFB staining in the CSF were noted in several older studies (96, 201). Some of the techniques included staining the clot that forms in standing CSF and spinning down the CSF sediment onto a slide for microscopic examination. The latter technique produced 91% sensitivity in 100 consecutive cases (201). In 1979, Kennedy and Fallon showed that staining multiple samples of CSF enhanced the sensitivity to 86% (96).

Several case series also established CSF culture sensitivities of 25 to 70% (97, 140). Samples from cisternal and ventricular CSF appear to have a higher culture sensitivity than conventional (lumbar puncture) CSF samples (233). A recent study established that both CSF volume and duration of the microscopic evaluation are independently associated with bacteriological confirmation of CNS tuberculosis, suggesting that a minimum of 6 ml of CSF fluid should be examined microscopically for a period of 30 min (215).

Molecular and Biochemical Analysis

The suboptimal and often delayed results from classical microbiological techniques traditionally used in the diagnosis of TBM underscore the need for a more rapid and accurate diagnostic method to facilitate early treatment. Several molecularly based techniques, often drawn from successful techniques used for the diagnosis of tuberculosis in respiratory specimens, have been evaluated for their applicability in the diagnosis of TBM. These techniques include commercially available nucleic acid amplification (NAA) methods and other PCR-based methods, antibody detection, antigen detection, or chemical assays such as adenosine deaminase (ADA) and tuberculostearic acid measurements. Among the challenges in evaluating the utility of these molecularly based diagnostic techniques is the reliance on clinical diagnosis for entry criteria, the relatively low numbers of patients included in the studies, and the myriad of different techniques, targets, collec-

TABLE 3. Performance of immunoassays for TBM[b]

Technique[a]	Population	% Sensitivity	% Specificity	Reference
Antibody assays				
ELISA	260 CSF samples (25 TBM, 235 non-TBM), India	72	92	159
ELISA	127 patients (29 TBM, 98 non-TBM), Philippines	52[c]	96	239
IFA	40 CSF samples, India	78	58	13
ELISA	198 patients (74 TBM, 124 non-TBM), India	61	100	33
ELISA (immunoglobulin G complexes)	67 patients (33 TBM, 34 non-TBM), India	64	91	130
ELISA and Western blotting	124 patients (30 TBM, 94 non-TBM), India	93	96	149
Passive hemagglutination assay and Western blotting	272 patients (88 TBM, 184 non-TBM), India	81	93	91
ELISA	53 patients (20 TBM, 33 non-TBM), India	80	91	89
ELISA	24 patients (12 TBM, 12 pulmonary TB), India	92	92	88
ELISA	74 patients (27 TBM, 49 non-TBM), China	52	92	164
Antigen assays				
Latex agglutination	152 children (18 TBM, 134 non-TBM), Greece	94	99	103
Reverse passive hemagglutination	216 patients (89 TBM, 127 non-TBM), India	88	95	32
Radioimmunoassay	75 patients (19 TBM, 56 non-TBM), India	79	100	82
Dot blot assay	63 (38 TBM, 25 non-TBM), Italy	92	100	125
Dot immunobinding assay	80 patients (40 TBM, 40 non-TBM), India	38	100	205
Dot immunobinding assay	80 patients (40 TBM, 40 non-TBM), India	63	100	202
Reverse passive hemagglutination and Western blotting	182 patients (51 TBM, 131 non-TBM), India	94	99	92
Immunostaining	44 patients (22 TBM, 22 non-TBM), India	73	100	203
Dot immunobinding assay	90 patients (45 TBM, 45 non-TBM), India	76	100	204
Dot ELISA	156 patients (56 TBM, 100 non-TBM), India	86	95	86

[a] Listed from oldest to newest.
[b] Data adapted from reference 93.
[c] Results involve a combined outcome of antibody and antigen testing.

tion methods, and purification modifications used, making the evaluation of tests that were not directly compared difficult. Clarity will likely not occur until each method has been optimized for their specific target and procedure and then compared head-to-head.

Antibody detection. While the detection of antibodies in the CSF to diagnose TBM is rapid, earlier studies evaluating the utility of measuring *M. tuberculosis*-specific antibodies in the CSF have shown that these techniques are limited by the inability to differentiate acute infection from previous infection and problems with cross-reactivity (91, 94) in addition to variable and often poor sensitivity and specificity (13, 33, 130, 149, 159, 239) (Table 3). An example of a more recent study shows that measuring antibodies against a 30-kDa protein that is a specific antigen of *M. tuberculosis* (88) yielded a more promising sensitivity of 92% (89). One technique that has emerged to address the suboptimal sensitivity of detecting *M. tuberculosis*-specific antibodies in the CSF is the use of immunospot assays to detect anti-*M. bovis* BCG antibody-secreting cells directly rather than quantifying the antibody itself (117, 164). In a study of patients with a clinical diagnosis of TBM that compared the utility of detecting anti-*M. bovis* BCG antibody-secreting cells in the CSF by enzyme-linked immunospot (ELISPOT) assay, PCR to detect an insertion sequence (IS*6110*) specific for *M. tuberculosis* in the CSF, and an enzyme-linked immunosorbent assay (ELISA) to detect anti-BCG antibodies, the ELISPOT method was more sensitive than (84% versus 75% and 52.3%, respectively) and as specific as (91.8% versus 93.7% and 91.6%, respectively) the other methods tested (164). Those authors also emphasized that the sensitivity of the ELISPOT method was better earlier in the clinical course of TBM and that the sensitivity improved to 100% among those tested within 4 weeks of onset of TBM symptoms (164).

Antigen detection. In addition to measuring *M. tuberculosis*-specific antibodies or antibody-secreting cells, assays to measure *M. tuberculosis*-specific antigens directly in the CSF have also been evaluated (32, 82, 86, 92, 103, 125, 202, 203, 205, 236) (Table 3). A theoretical advantage of antigen detection over antibody detection would be that they would be released only as a result of the host's immune response or the result of treatment. In a study among patients with a clinical diagnosis of TBM that compared a dot immunobinding assay for an *M. tuberculosis*-specific 14-kDa protein antigen with PCR to detect IS*6110*, specific for *M. tuberculosis* in the CSF, the immunobinding assay was more sensitive than the PCR method (75% versus 40.5%, respectively) (204). Among the advantages of either antibody or antigen detection methods is that these methods are more applicable to laboratories based in the developing world, where the majority of the TBM burden remains, than more costly PCR-based methods (164, 204).

Molecular methods. The challenges of applying NAA techniques to the rapid diagnosis of *M. tuberculosis* in the CSF stem largely from the low number of bacilli typically present in TBM and the presence of amplification inhibitors in the CSF. Two commercially available methods of NAA for the direct detection of the *M. tuberculosis* complex have been approved in the United States for testing of respiratory specimens: the Amplified *Mycobacterium tuberculosis* Direct Test (MTD; GeneProbe, Inc., San Diego, CA) and the Amplicor *Mycobacterium tuberculosis* Test (Roche Diagnostic Systems, Inc., Indianapolis, IN). No NAA methods have been approved for testing of

TABLE 4. Performance of PCR-based assays for the diagnosis of TBM

Technique[a]	Population	% Sensitivity	% Specificity	Reference
Commercially available NAA assays				
Modified Gen-Probe MTD	6 TBM specimens, Switzerland	100	96	154
Roche Amplicor MTB PCR	69 patients (40 TBM, 29 non-TBM), South Africa	60	100	24
Modified Gen-Probe MTD	84 children (24 TBM, 60 non-TBM), Dominican Republic	83	100	110
Gen-Probe MTD	311 specimens, Canada	94[b]	99[b]	35
Meta-analysis	14 studies with commercial NAA assays	56	98	146
Modified Gen-Probe MTD	27 CSF specimens spiked with *M. tuberculosis*	17–100	100	38
Modified BDProbeTec ED	13 culture-positive specimens, Denmark	77[b]	99[b]	81
Other PCR-based assays				
In-house PCR	26 patients (6 TBM, 20 non-TBM), Japan	83	100	83
In-house PCR	85 patients (34 TBM, 51 non-TBM), India	65	88	193
In-house PCR	67 CSF samples (43 TBM, 24 non-TBM), South Africa	63	100	54
In-house PCR	25 AIDS patients (11 TBM, 14 non-TBM)	82	100	59
MPB64 PCR	19 patients (6 TBM, 13 non-TBM), Singapore	83	92	111
IS*6110* PCR	27 patients (6 TBM, 21 non-TBM), Singapore	100	38	112
In-house PCR	20 patients (10 TBM, 10 non-TBM), Brazil	70	100	120
IS*6110* PCR	42 patients (24 TBM, 18 non-TBM), The Netherlands	48	100	102
IS*6110* nested PCR	36 AIDS patients (12 TBM, 24 non-TBM)	100	100	180
In-house PCR	136 TBM patients, Vietnam	32	100	141
In-house PCR	89 patients (40 TBM, 49 non-TBM), India	85	94	189
IS*6110*/MTP40 PCR	11 patients (5 TBM, 6 non-TBM), China	60	66	240
Cobas Amplicor TB PCR	69 patients (40 TBM, 29 non-TBM), South Africa	18	100	23
IS*6110* PCR	131 TBM patients, United Kingdom	75[b]	94[b]	30
MPB64 nested PCR	47 pleural and CSF samples, Brazil	70[b]	88[b]	123
MPB64 nested PCR	91 patients (41 TBM, 50 non-TBM), Brazil	53	100	25
TRC_4 PCR	96 children (67 TBM, 29 non-TBM), India	91	76	137
In-house PCR	120 (105 TBM, 15 non-TBM), India	31	100	46
In-house PCR	56 TBM patients, Kenya	4.3[b]	100[b]	68
In-house PCR	29 TBM patients, Iran	86[b]	100[b]	165
In-house PCR	60 children (30 TBM, 30 non-TBM), India	90	100	104
In-house PCR	57 TBM patients, India	67[b]	100[b]	45
IS*6110* PCR	74 patients (25 TBM, 49 non-TBM), China	75	94	164
IS*6110* PCR	677 TBM patients, India	76	89	166
IS*6110* PCR	176 patients (101 TBM, 75 non-TBM), India	98[b]	100[b]	167
QNRT-PCR[c]	43 samples from 8 TBM patients, 20 non-TBM, Japan	56	100	210

[a] Listed from oldest to newest.
[b] Results versus culture as the gold standard.
[c] QNRT-PCR, quantitative nested real-time PCR.

CSF, but several studies have evaluated their performance in TBM cases (9, 35, 110) (Table 4). A recent meta-analysis of the accuracy of NAA in diagnosing TBM revealed a sensitivity of 56% (negative predictive value [NPV], 44%) and a specificity of 98% (positive predictive value [PPV], 35.1%) among commercially available NAA assays, suggesting that they may play a role in confirming TBM, but because of its low sensitivity, it is not ideal for ruling out TBM (146). In at least one study, the use of the MTD test was not helpful in diagnosing tuberculoma (9). Recently, several modifications to the MTD test have been attempted to improve the performance of testing for *M. tuberculosis* in the CSF (38, 81, 154). One scenario in which NAA assays may play an important role is in assisting the diagnosis of TBM after empirical antituberculosis therapy has begun, since the sensitivity of these methods persists longer than conventional bacteriology after therapy has been initiated (213).

Beyond the commercially available NAA methods, the application of PCR methods to amplify mycobacterial DNA has received abundant attention (Table 4). Experimentally, PCR assays are able to detect *M. tuberculosis* DNA down to an estimated 2-CFU/ml concentration (10). Many of these assays utilize primers directed at the insertion sequence IS*6110* (30, 77, 102, 137, 166, 167, 180, 240), which is a repetitive element exclusively found in the genome of the *M. tuberculosis* complex (230), although isolates with low copy numbers and even no copy numbers have been identified (230). A recent example of this method includes the use of an IS*6110* uniplex PCR assay that had 98% sensitivity (NPV, 99%) and a specificity of 100% (PPV = 100%) against the "gold standard" of culture (167) and an overall sensitivity of 76.4% (NPV, 59.9%) and specificity of 89.2% (PPV, 94.7%) when clinical TBM was included (166). Several methods of PCR have been evaluated, including quantitative nested real-time PCR (208–210), the Amplicor *Mycobacterium tuberculosis* Test (23, 24), and a variety of other in-house PCR assays (45, 46, 51, 83, 104, 111, 120, 123, 138, 141, 165, 189, 193). These assays have been evaluated specifically in HIV-coinfected patients (59, 180) and also as a means to monitor therapy (180, 210). While many of those studies demonstrated improved sensitivity over traditional smear and culture methods, several other studies highlighted the low sensitivities associated with these PCR assays (25, 68, 112, 164, 206). Looking at the utility of applying PCR assays to the

TABLE 5. Performance of biochemical assays for TBM

Technique[a]	Population	% Sensitivity	% Specificity	Reference
ADA assays				
Cutoff, ≥6.0 IU/liter	134 CSF samples (24 TBM, 110 non-TBM), South Africa	92	98	21
Cutoff, ≥10.0 U/liter	101 pediatric patients (38 TBM, 63 non-TBM), South Africa	73	71	40
Cutoff, ≥5.0 IU/liter vs aseptic meningitis	97 patients (34 TBM, 63 non-TBM), South Africa	70	99	48
Cutoff, ≥10.0 U/liter vs aseptic meningitis	346 adult CSF samples, Spain	48[b]	100[b]	116
Cutoff, ≥5.0 IU/liter vs pyogenic	35 pediatric patients (27 TBM, 8 pyogenic), India	63	89	132
Cutoff, ≥9.0 IU/liter	119 patients (14 TBM, 105 non-TBM), Malaysia	100	88	176
Cutoff, ≥5.0 IU/liter	66 pediatric patients (27 TBM, 39 non-TBM), India	89	92	131
Cutoff, ≥8.0 IU/liter	60 patients (36 TBM, 24 non-TBM), India	44	75	62
Cutoff, ≥7.0 U/liter vs viral	182 patients (36 TBM, 9 pyogenic, 130 viral, 7 cryptococcal), South Korea	83 (vs viral)	95 (vs viral)	36
Cutoff, ≥10.0 U/liter vs pyogenic		58 (vs pyogenic)	89 (vs pyogenic)	
Cutoff, ≥11.39 U/liter/min	281 patients (171 culture confirmed, 41 pyogenic, 19 viral, 104 controls), India	82	83	87
Tuberculostearic acid assays				
Gas chromatography and mass spectrometry	13 culture confirmed cases; (9 suspected cases); 87 negative controls	100 (89)	99	61
Gas-liquid chromatography	41 culture confirmed cases (Cairo, Egypt); 75 clinical cases (United States, Canada)	95	91	26

[a] Listed from oldest to newest.
[b] Results for TBM or neurobrucellosis.

diagnosis of tuberculoma, in one small study, immunohistochemical techniques outperformed PCR methods conducted on surgically removed tuberculomas (206).

While commercially available NAA and other PCR assays may not provide a perfect screening tool for the diagnosis of TBM, they appear to be useful as a supplement to conventional approaches and may be especially useful either once antituberculosis therapy has begun or as a method for monitoring treatment response. However, like any diagnostic test for tuberculosis, a negative result cannot exclude the possibility of tuberculosis, and clinical judgment remains paramount. An additional challenge of using PCR-based methods in the diagnosis of TBM is the requirement of appropriate laboratory infrastructure to perform these more sophisticated methods, infrastructure that is often lacking in areas where TBM is highly endemic.

ADA. ADA is an important enzyme in purine metabolism, which irreversibly deaminates adenosine, converting it to inosine. The presence of ADA is associated largely with lymphocytic proliferation and differentiation and is considered to be a marker of cell-mediated immunity (87). ADA is comprised of two different isoforms, ADA1 and ADA2. ADA1 is present throughout many tissues but appears to be most important functionally in lymphocytes and macrophages. ADA2 is almost exclusively identified in macrophages and is elevated in a variety of infections and diseases involving the immune system. Several studies have been performed to evaluate the utility of ADA measurements in the CSF to improve the diagnosis of TBM (21, 36, 40, 48, 62, 87, 116, 131, 132, 176). The measured sensitivities and sensitivities range from 44 to 100% and 71 to 100%, respectively (Table 5). While some of the studies showed statistically significant differentiation from aseptic meningitis and bacterial meningitis, several other studies could not demonstrate a distinction between TBM and bacterial meningitis by ADA alone (48, 62), and in one study, ADA was not valuable in distinguishing TBM in patients with HIV infection (41). Additionally, standardized cutoffs of ADA values for the diagnosis of TBM have not been established, and the values used in the various studies ranged from >5.0 to >15 IU/liter, making the practical use of this assay more difficult. CSF ADA measurements have been found to be useful in predicting poor neurological outcomes among pediatric TBM cases (76). It has also been established that isotype ADA2 is the major contributor to the total ADA seen in TBM (the same is true for bacterial meningitis) (187).

Tuberculostearic acid. Tuberculostearic acid is a fatty acid component of the *M. tuberculosis* cell wall, which has been detected in CSF of patients with TBM via various forms of gas chromatography (26, 61, 121). Although this method has good sensitivity and specificity in limited studies (Table 5), the requirement for expensive equipment and considerable expertise has limited the clinical use of this technique.

Radiographic Assessments

While the use of neuroradiographic techniques such as computer tomography (CT) and magnetic resonance imaging (MRI) have vastly improved the diagnostic accuracy of TBM and tuberculomas, no series of radiographic findings are pathognomonic for CNS TB. The role of neuroradiographic techniques in the evaluation of CNS tuberculosis was recently reviewed elsewhere (16). Commonly identified neuroradiological features of TBM include basal meningeal enhancement, hydrocephalus, and infarctions in the supratentorial brain paren-

TABLE 6. Guidelines for the treatment of CNS tuberculosis[a]

Drug	Pediatric daily dose	Adult daily dose	Duration (mo)	CNS penetration
First-line therapy				
Isoniazid	10–15 mg/kg (300 mg)	5 mg/kg (300 mg)	9–12	Yes
Rifampin	10–20 mg/kg (600 mg)	10 mg/kg (600 mg)	9–12	Yes, with inflammation
Rifabutin	Unknown	5 mg/kg (300 mg)	9–12	Yes, with inflammation
Pyrazinamide	15–30 mg/kg (2.0 g)	15–30 mg/kg[b] (2.0 g)	2	Yes
Ethambutol	15–20 mg/kg (1.0 g)	15–20 mg/kg[b] (1.0 g)	2	Yes, with inflammation
Second-line therapy				
Cycloserine	10–15 mg/kg/day (1.0 g/day)	10–15 mg/kg/day (1.0 g/day)	18–24	Yes
Ethionamide	15–20 mg/kg/day (1.0 g/day)	15–20 mg/kg/day (1.0 g/day)	18–24	Yes
Streptomycin[c]	20–40 mg/kg/day (1.0 g)	15 mg/kg/day (1.0 g), 10 mg/kg/day in patients >59 yr of age (750 mg)	6	Yes, with inflammation
Amikacin-kanamycin[c]	15–30 mg/kg/day (1.0 g)	15 mg/kg/day (1.0 g), 10 mg/kg/day in patients >59 yr of age (750 mg)	6	Yes, with inflammation
Capreomycin[c]	15–30 mg/kg/day (1.0 g/day)	15 mg/kg/day (1.0 g), 10 mg/kg/day in patients >59 yr of age (750 mg)	6	Yes, with inflammation
p-Aminosalicylic acid	200–300 mg/kg/day in 2 to 4 divided doses (10 g)	8–12 g/day in 2 or 3 divided doses	18–24	Yes, low levels
Levofloxacin	Unknown[d]	500–1,000 mg	18–24	Yes, low levels
Moxifloxacin	Unknown[d]	400 mg	18–24	Yes, low levels
Gatifloxacin	Unknown[d]	400 mg	18–24	Yes, low levels

[a] Data adapted from reference 3; maximum doses are in parentheses.
[b] See reference 3 for suggested doses.
[c] Intravenous route only.
[d] Long-term use of fluoroquinolones in children has not been approved.

chyma and brain stem (16). While there has been some concern about the ability of radiographic imaging to identify TBM findings in HIV-coinfected patients (90), others reported no difference in radiographic findings among HIV-infected and noninfected patients (234).

Contrast-enhanced MRI is generally considered to be superior to CT in detecting and assessing CNS tuberculosis (16, 80, 100, 142). While MRI is arguably superior to CT in identifying meningeal and parenchymal abnormalities, its limited availability worldwide and the requirement for general anesthesia in children suggest that it may have a limited impact on TBM diagnosis globally (5).

In an attempt to establish CT criteria for the diagnosis of CNS tuberculosis, Kumar et al. identified basal meningeal enhancement, ventriculomegally, tuberculoma, and infarcts as characteristics to distinguish CNS tuberculosis from pyogenic meningitis and proposed that basal meningeal enhancement, tuberculoma, or both were 89% sensitive and 100% specific for TBM (107). Andronikou et al. suggested that several specific characteristics of basal meningeal enhancement, which is found in up to 90% of pediatric TBM cases (107), were important for identifying TBM in children (4). Przybojewski et al. evaluated nine of these distinct CT criteria for basal meningeal enhancement and suggested that the presence of four criteria were highly specific and that having more than one criteria was 91% sensitive for TBM (162). Assessment of treatment response radiographically is challenging in TBM due to the variability of that response. Healing may be seen as an absence of basal meningovascular enhancement, although some patients may demonstrate an initial increase in the amount of basal meningeal enhancement, while others may show persistent enhancement despite adequate therapy (16). Long-term sequelae of TBM may include meningeal calcifications and focal areas of atrophy (16).

Tuberculomas are normally defined as low- or high-density, round or lobulated masses with irregular walls and show homogenous or ring enhancement after administering contrast (93) (Fig. 2). They occur as solitary or multiple nodules and typically are found in the frontal and parietal lobes (93). The "target sign" (central nidus of calcification surrounded by a ring of enhancement) was once considered to be pathognomonic for tuberculoma (16), but this has recently been called into question (11). The radiographic presentation of tuberculomas depends largely on whether the lesion is noncaseating, caseating with a solid center, or caseating with a liquid center; the degree of edema surrounding the tuberculoma is thought to be inversely proportional to the age of the lesion (16). Other radiographic techniques such as magnetic resonance spectroscopy have been shown to help distinguish tuberculoma from cysticercosis (161) but not from non-Hodgkin lymphoma of the CNS (78). Once diagnosed, the radiographical response of tuberculoma to therapy can generally be assessed within 4 to 6 weeks (16). While new or enlarging tuberculoma may occur in some patients despite adequate antituberculosis therapy, the activity of tuberculoma can generally be assessed by the degree of contrast enhancement on follow-up CT or MRI studies (16). Late radiographical changes in tuberculomas include calcifications, local atrophy, or no residual radiological abnormalities. Tuberculous brain abscesses cannot be reliably differentiated radiographically from pyogenic abscesses and generally require surgical intervention for microbiological diagnosis.

TREATMENT, PROGNOSIS, AND PREVENTION

Antibiotic Therapy

The standard approach to CNS tuberculosis, endorsed by Infectious Diseases Society of America, Centers for Disease

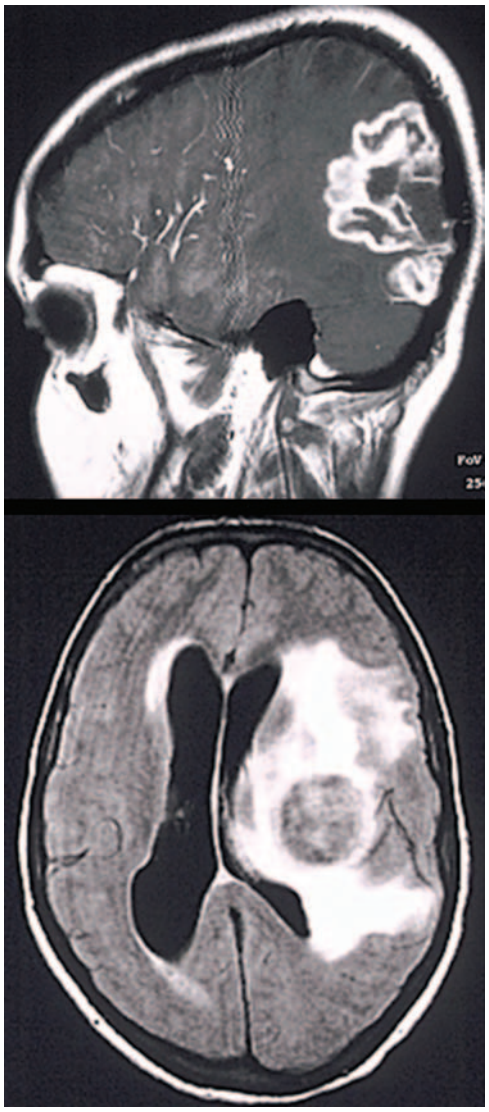

FIG. 2. MRI of CNS tuberculoma. Contrast-enhanced scans show CNS tuberculoma.

Control and Prevention, and American Thoracic Society guidelines (3) (Table 6), includes an initial 2-month induction therapy regimen including isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 7 to 10 additional months of isoniazid and rifampin as maintenance therapy for an isolate that is sensitive to these agents. Isoniazid, rifampin, and the second-line agents aminoglycosides, capreomycin, and fluoroquinolones are available in parenteral form if an altered mental status precludes oral intake. The recommended use of this regimen and the duration of therapy are extrapolated from the standard regimen for pulmonary tuberculosis, since no randomized control trial has established an optimal treatment course for CNS tuberculosis. The obvious difficulty in conducting such trials stems largely from the relative rarity of TBM, the difficulty of early diagnosis, and the high mortality in advanced cases. Some have advocated for longer treatment (64, 66), while others have supported a short course of 6 to 9 months (50, 74, 156, 228). Both isoniazid and pyrazinamide pass easily across the BBB (54, 55, 84, 155), and isoniazid remains the backbone of TBM treatment. Rifampin and ethambutol have significantly less penetration into the CNS (54, 84), although they still play an important role in the treatment of CNS tuberculosis (139).

While the importance of multiply drug-resistant (MDR) tuberculosis (defined by resistance to both isoniazid and rifampin) has been well documented in the literature, the features of MDR tuberculosis in TBM have been characterized mostly by case reports and small case series (17, 28, 29, 44, 47, 69, 145, 148, 196, 199, 200, 238). With MDR tuberculosis, time to identification of resistance is often prolonged, and therefore, time to appropriate antituberculosis therapy is delayed (up to 10 weeks) or even initiated after the disease has advanced too far (145, 148). In some of the published series, the Medical Research Council grading system was not predictive in MDR TBM cases (145, 148). Although the mortality among these MDR TBM cases is quite high, many of the patients never actually received adequate therapy prior to their demise (145, 148). MDR tuberculosis therapy should be considered if there is a history of prior tuberculosis treatment, contact with a patient with MDR tuberculosis, or a poor clinical response to first-line TB therapy within 2 weeks despite a firm diagnosis and an adequate adherence to treatment. Much like the treatment of standard TBM, without controlled trials, the treatment of MDR TBM is based largely on experience in the treatment of MDR pulmonary tuberculosis, which in itself lacks sufficient evidence-based support (3) (Table 6). Second-line agents such as aminoglycosides penetrate the BBB only in the presence of inflamed meninges, and fluoroquinolones, while able to penetrate into the CNS, have lower CSF levels than in the serum or brain parenchyma (17, 47). With the emergence of extensively drug-resistant (XDR) tuberculosis (defined by resistance to isoniazid, rifampin, fluoroquinolones, and either capreomycin, kanamycin, or amikacin), even these second-line agents will be ineffective. Second-line agents such as ethionamide (which is structurally similar to isoniazid) and cycloserine have good CNS penetration and may be among the only agents available to begin building a treatment regimen for XDR TBM. It has been suggested that even in the presence of isoniazid resistance, it should still be a part of the TBM treatment regimen (218). Intrathecal administration of antituberculosis agents has also been reported (17, 199). Finally, in regions where it is feasible, the use of therapeutic drug monitoring may assistant in the management of MDR TBM cases (47, 151).

Adjunctive Steroid Therapy

The use of corticosteroids as adjunctive therapy in the treatment of CNS tuberculosis began as early as the 1950s (192) and remains to this day a controversial issue. The initial rationale behind the use of steroids included the reduction of inflammation within the subarachnoid space (144). Concerns regarding impairment of cellular defense against *M. tuberculosis* and the potential reduction of drug penetration into the CNS have always surrounded the use of corticosteroids in this manner. At least in the case of first-line antituberculosis therapy, there does not appear to be any difference in drug penetration into the CSF with or without corticosteroid therapy (84).

In an attempt to clarify the benefits of adjunctive corticoste-

roid use in TBM, a meta-analysis by Prasad et al. found that steroid use was associated with fewer deaths, but this effect was noted only for children, and that much of the evidence favoring the use of steroids was limited to studies with small sample sizes and may be a result of publication bias (160). Since then, a large placebo-controlled trial of dexamethasone as adjunctive therapy of TBM in Vietnam by Thwaites et al. identified a significant reduction in mortality but not in morbidity in adults (220). Further subgroup analyses revealed that the mortality benefit of dexamethasone occurred among all severity types of CNS tuberculosis but that this benefit did not extend to patients coinfected with HIV (220). That study went a long way in resolving the controversy over the benefit of adjunctive dexamethasone therapy in CNS tuberculosis. Current Infectious Diseases Society of America, Centers for Disease Control and Prevention, and American Thoracic Society guidelines (3) endorse the use of steroid therapy as an adjunctive therapy coupled with standard antituberculosis therapy in CNS tuberculosis. The recommended regimen is dexamethasone in an initial dose of 8 mg/day for children weighing less than 25 kg and 12 mg/day for children weighing 25 kg or more and for adults (63). The initial dose is given for 3 weeks and then decreased gradually during the following 3 weeks. The more recent placebo-controlled trail by Thwaites et al. used an initial dose of 0.3 mg/kg/day for grade I and 0.4 mg/kg/day for grades II and III, followed by a gradual taper over 6 weeks (220, 222).

The mechanism by which dexamethasone exerts its survival benefit is currently unclear. Two broad mechanisms have been evaluated: (i) the effect of dexamethasone on the deleterious aspects of the immune response in the CNS and (ii) the ability of dexamethasone to prevent hydrocephalus and/or infarction. In children with CNS tuberculosis, despite no difference in CSF cell counts, adjunctive corticosteroid therapy was associated with lower protein and globulin and higher glucose levels sooner than in those not receiving corticosteroids (182), suggesting some immune modification. However, thalidomide (a potent TNF-α inhibitor) failed to demonstrate a beneficial effect on TBM in children (185). Another possible mechanism of immune modification that may be involved is that corticosteroids influence the response of microglial cells, which are the resident macrophages in the CNS and are the only cells productively infected in the brain (173). Our laboratory examined the effect of dexamethasone therapy on the production of proinflammatory cytokines and chemokines by *M. tuberculosis*-infected microglial cell cultures (174). In those experiments, *M. tuberculosis*-infected microglia elicited robust amounts of several cytokines and chemokines including TNF-α, IL-6, IL-1β, CCL2, CCL5, and CXCL10. Treatment with dexamethasone markedly suppressed the production of these mediators. With these data in mind, we proposed that the mortality benefits of dexamethasone could operate via modulation of the local production of proinflammatory cytokines and chemokines by microglial cells in the microenvironment where *M. tuberculosis* is replicating and residing. In an effort to evaluate whether dexamethasone benefits patients by influencing measurable immune responses in the CSF, Simmons et al. reported that while dexamethasone reduced CSF protein concentration and marginally reduced measurable gamma interferon levels compared to those not receiving dexamethasone, there were no measurable differences in measured cytokines, chemokines, CSF mononuclear phenotypes, peripheral T-cell responses, and other CSF fluid parameters, suggesting that dexamethasone's effects are not attributable to altering the immune response in the CSF (197). However, it is possible that the potential benefits of anti-inflammatory agents such as dexamethasone are related to effects within the brain parenchyma, which may not be reflected in the CSF. Looking at the impact of dexamethasone on hydrocephalus and infarction, Schoeman et al. reported that steroids did not appear to affect intracranial pressure or the extent of infarction in children despite having a positive influence on survival (186). Recently, Thwaites et al. used serial MRI to assess the effect of dexamethasone on hydrocephalus, basal meningeal enhancement, the presence of tuberculoma, and infarction, and they were unable to demonstrate that dexamethasone influenced any of these parameters as well (219).

So for now, the manner in which dexamethasone affects the neuropathogenesis of CNS tuberculosis remains unknown, but the benefit clearly extends to children and adults with CNS tuberculosis. Further research will need to address whether this same benefit extends to patients coinfected with HIV.

Surgical Therapy

Since the development of effective antituberculosis therapy, the role of surgery has revolved largely around dealing with the serious complication of hydrocephalus, reducing the mass effect of tuberculomas, and draining brain abscesses. Although the etiology is not entirely known, hydrocephalus is thought to be the result of basal meningitis wherein the flow of CSF is blocked in its course from the exit site in the fourth ventricle to the site of its absorption in the arachnoid villi or possibly the destruction of the arachnoid villi themselves (65). Hydrocephalus is an extremely common complication of CNS tuberculosis and can be treated with diuretics, osmotic agents, serial lumbar punctures, external ventricular drainage, or ventriculoperitoneal shunts (VPS). Assessment of hydrocephalus is considerably harder in young children than in adolescents and adults. Imaging and intracranial pressure monitoring are often critical for evaluating for hydrocephalus (183). The method that is most effective for treating TBM-associated hydrocephalus has not been specifically studied to date. For individuals with communicating hydrocephalus, the addition of acetazolamide and furosemide to standard antituberculosis therapy is superior to antibiotics alone (181). For those with noncommunicating hydrocephalus, some form of external drainage and/or VPS is needed. The role of VPS and the timing of its use in children are controversial. Several groups have advocated performing VPS early in the clinical course of hydrocephalus, especially in mild- to moderate-grade cases (grade I/II/III according to the neurosurgical grading system described by Palur et al.) (147) and performing a trial of external drainage in extremely poor-grade cases (grade IV cases) (95, 126, 147), whereas others endorse VPS only for those with noncommunicating hydrocephalus or those failing antibiotic therapy with communicating hydrocephalus (109, 183). When the role of VPS has been examined for TBM-associated hydrocephalus, success rates ranged between 40 to 50%, and VPS has a complication rate of around 30% (1, 109). Given the poor outcomes for individuals coinfected with HIV, some have questioned the utility of VPS

in this population and instead advocated a trial of external drainage prior to any further intervention (136). More recently, there are encouraging data on the safety and efficacy of neuroendoscopy in relieving hydrocephalus in both adults (72) and infants (245), which may negate the need for VPS.

The role of surgery for tuberculomas has been eclipsed largely by the use of conventional antituberculosis therapy and corticosteroids and is reserved essentially for treatment failures or when the diagnosis is in doubt. Appropriate treatment options for tubercular abscesses include simple puncture, continuous drainage, fractional drainage, repeated aspiration through a burr hole, stereotactic aspiration, and total excision of the abscess (108).

Prognosis and Outcomes

Initial improvement of clinical symptoms may be quite slow and may in fact briefly worsen despite appropriate antituberculosis therapy (207). The development of new tuberculoma while receiving antituberculosis therapy for TBM has also been repeatedly reported in case series and case reports (2, 73, 114, 115, 135, 150, 190, 195, 211, 237, 243). Assuming that the level of diagnostic certainty is high, such developments do not necessitate altering the treatment strategy in most cases, with the possible exception of prolonging the use of steroids in the regimen, which at least anecdotally may mitigate these unwanted sequelae. Because the development of sequelae such as hydrocephalus may also be delayed, close monitoring following the initiation of antituberculosis therapy is often needed. Follow-up CT scans at 1 week and 1 month after the initial CT scan have been shown to be particularly important in picking up important diagnostic findings and adverse sequelae in children with CNS tuberculosis (6).

The mortality rate associated with treated TBM is 20 to 50% in several series (63, 64, 74, 96, 97, 143, 220). In a large series from Egypt, 1,430 TBM patients were evaluated from 1976 to 1996, and the mortality rate was 57% (64). From this series, those authors observed that the initial stage of disease at presentation was a major prognostic indicator for mortality. In their series, the mortality rate was 18% for stage I TBM, 34% for stage II, and 72% for stage III. The importance of the stage of disease in predicting outcome has been well documented in other series as well (74, 97, 220). Additionally, patients presenting after 4 weeks of symptoms had 80% mortality, whereas those presenting with less than 2 weeks of symptoms had 40% mortality (64). Even the large dexamethasone trial by Thwaites et al. had 31.8% mortality in the steroid-treated arm, with mortality rates diverging depending on the presenting stage of disease (stage I, 16.7%; stage II, 31.1%; stage III, 54.8%) (220). Among the survivors of TBM, some form of neurological impairment afflicts approximately 20 to 30%. These impairments range from cranial nerve palsies, ophthalmoplegia, seizures, psychiatric disorders, and ataxia to hemiparesis, blindness, deafness, and mental retardation. Poor neurological outcomes again can also be predicted based the presenting stage of disease (63, 64, 74, 96, 97, 143, 220).

Researchers seeking additional predictors of poor outcome in CNS tuberculosis, specifically in children, identified advanced stage of the disease at presentation (71), age (71), and the presence of any infarction other than a purely hemispheric infarction (7) as important predictors. Studies that included primarily adults identified the stage of disease (64, 214), HIV coinfection (217), the combination of isoniazid and rifampin resistance (218), and CSF parameters such as high CSF lactate, CSF leucopenia, and low CSF glucose (221) as being poor prognostic indicators. Misra et al. studied both children and adults and identified stage, age, focal weakness, cranial nerve palsies, and hydrocephalus as predictors of mortality at 3 months (133). Interestingly, features such as presenting intracranial pressure (184), cytokines in the CSF (198), isoniazid or streptomycin resistance (214), and *M. tuberculosis* genotype (122) have been shown not to be predictive of a poor outcome.

Prevention

The debate surrounding the efficacy of the bacillus Calmette Guerin (BCG) vaccine has been ongoing since it was first developed by Albert Calmette and Camille Guerin in 1921. Currently, BCG vaccination covers 85% of newborn infants, and it has been estimated that nearly 100 million children are vaccinated with BCG vaccine every year (12). Several studies have shown that BCG protects against TBM and that its efficacy is around 75 to 85% (8, 18, 27, 34, 105, 129, 163, 188, 194, 212, 244, 248). Two recent meta-analyses also concluded that BCG vaccination protects against TBM (39, 175). The efficacy of BCG appears to persist through 10 years after infant vaccination (39). A recent cost-benefit analysis estimated that one case of TBM will be prevented with every 3,435 BCG vaccinations provided to infants and was deemed highly cost-effective (223). This benefit is postulated to be the highest in Southeast Asia, where the risk of tuberculosis and the use of BCG vaccination are highest. However, several other studies have raised concerns that nutritional status may be confounding these beneficial results (8), that BCG vaccination simply delays the onset of TBM (134), that discontinuing BCG vaccination programs has no impact on TBM rates (247), and that vaccinating children has little impact on the clinical presentation of TBM among those that ultimately develop TBM (67). This last point has recently been addressed in a prospective trial by Kumar et al., which showed that BCG-vaccinated children who do develop TBM have a milder clinical course and better short-term outcomes than do their unvaccinated counterparts, which those authors speculated is attributable to a better immunological response induced by BCG vaccination (106).

Overall, BCG vaccination appears to have sufficient efficacy to justify ongoing vaccination programs in areas where tuberculosis is highly endemic, and even when TBM develops, BCG vaccination appears to mitigate the severity of the condition. However, like all vaccinations, efficacy is not 100%, and a history of BCG vaccination does not eliminate the need to investigate the possibility of TBM in the right clinical situation.

FUTURE RESEARCH NEEDS

Overcoming the considerable challenges that are inherent in diagnosing, treating, and managing CNS tuberculosis will require an equal measure of ingenuity and resourcefulness to improve outcomes. Further insights into the basic neuropathogenesis of *M. tuberculosis* through the use of basic science techniques and the development of a relevant animal model

are desperately needed to advance our understanding of the disease and uncover potential avenues for intervention. Standardization of promising molecular diagnostic techniques currently available and the development of new methods which are sensitive to the limited resources available in areas of high endemicity are needed to improve the pace and accuracy of diagnosis. An understanding of how corticosteroids improve survival may lead to novel adjunctive treatments, and an evaluation of whether their benefit extends to HIV-infected individuals is needed to maximize their potential value as adjunctive agents. Similar to the need for a rapid identification of drug resistance in *M. tuberculosis* isolates in general, the application of these methods to CNS tuberculosis could profoundly reduce the delay in adequate therapy for those with resistant isolates. With the continued identification of MDR TBM cases and the emerging incidence of XDR isolates (85, 170, 229), a new sense of urgency to develop methods for the rapid identification of resistance has emerged. As with tuberculosis in general, the development of well-tolerated and effective antibiotics remains a continued need. Drugs which possess the ability to cross the BBB and achieve therapeutic concentrations in the CSF and brain parenchyma would be specific qualities in drug development for TBM. Further studies to assess the optimal regimen and length of treatment would also assist in managing patients using the currently available tools. Ultimately, developing new vaccine strategies or improving upon the existing BCG vaccines currently in use may prove to have the most significant impact on CNS tuberculosis worldwide, with the promise of truly limiting or eliminating manifestations of tuberculosis in the CNS.

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